# Motherisk Update

## Pregnant "DES daughters" and their offspring

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**ABSTRACT**

**QUESTION** I am a 34-year-old woman in my second trimester of pregnancy. My mother took diethylstilbestrol when she was pregnant with me. Could my expected child be affected by this?

**ANSWER** Animal studies suggest the child could be affected, but little data on humans strongly support this. You could plan to have your child monitored for a potential, though unlikely, effect.

**RÉSUMÉ**

**QUESTION** Je suis une femme de 34 ans et j'en suis à mon deuxième trimestre de grossesse. Ma mère a pris du diéthylstilboestrol lorsqu'elle était enceinte de moi. L'enfant que je porte pourrait-il en être affecté?

**RÉPONSE** Des études sur les animaux donnent à croire que l'enfant pourrait en être affecté mais très peu de données concernant les humains appuient cette conclusion de manière convaincante. Vous pourriez prévoir de faire vérifier votre enfant pour détecter des effets possibles mais peu probables.

Diethylstilbestrol (DES) is a potent synthetic estrogen widely prescribed to pregnant women between 1938 and 1971 to improve outcome of pregnancy.[1] Results of several epidemiologic studies in the early 1970s showed that use of DES during pregnancy was associated with a substantial increase in vaginal and cervical clear-cell adenocarcinoma and genital tract abnormalities in adolescent girls exposed to DES in utero.[2,3] There was also an increased risk of first- and second-trimester spontaneous abortions, ectopic pregnancies, and preterm deliveries among daughters who had been exposed.[4]

An association between in utero exposure to DES and abnormalities of men's urogenital systems was also found.[5,6] The most common abnormalities are epididymal cysts, undescended testes, and small testes. A recent study suggested an increased incidence of testicular cancer among men exposed in utero to DES.[7]

When early reports of increased frequency of uterine and ovarian adenocarcinoma in offspring of mice exposed in utero to DES were first published in the mid-1980s,[8,9] they raised concern regarding possible adverse effects on the third generation of humans exposed to DES.

A study of 28 daughters (mean age 20 years) of women exposed to DES in utero showed that these third-generation women had no abnormalities of the genital tract, and no cases of endometrial, ovarian, cervical, or vaginal carcinoma, or intraepithelial neoplasia of the cervix or vagina were detected.[10] Review of their mothers' records indicated that 61.5% of the mothers exposed to DES in utero had structural changes of the cervix, upper vagina, or vaginal epithelium. The main limitations of this study were the small sample size and the age of the women, who might have been too young to reflect the true rate of subsequent genital malignancies.

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The absence of abnormalities of the lower genital tract in third-generation women compared with the high frequency of these abnormalities in their mothers suggests that third-generation carry-over effects of DES exposure are rare.

A recent case report of an ovarian malignancy in a third-generation adolescent[11] raised the possibility of an association between her malignancy and her grandmother's use of DES. The authors described a 15-year-old girl with small cell carcinoma of the ovary whose maternal grandmother had been taking DES while she was pregnant with the patient's mother. Although this is an anecdotal case, the rarity of this disorder suggests that DES exposure could have a trans-generational effect.

An increased rate of hypospadias has recently been reported in third-generation men. A Dutch cohort study compared 205 sons of women who were exposed to DES in utero with 8934 men with no such history. Four (2%) of the exposed sons had hypospadias, compared with nine (0.01%) in the control group.[12]

Differences between human and mice models in the effects of DES on the third generation suggest that the effect observed in mice is much greater than in humans. Nevertheless, some authors recommend that third-generation women should be examined carefully for presence of DES-associated changes.[10]

A variety of theories have been proposed for the mechanism of action of multi-generational effects of DES. In mice, the carcinogenicity of DES can apparently be transmitted from prenatally exposed offspring to the next generation. Germ cell mutation has been implicated as the mode of transmission of the genotoxic effect.[9] Imprinting might be another mode of transmission.

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## MOTHERISK

**Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Drs Schechter and Finkelstein are members and Dr Koren is Director of the Motherisk Program. Dr Koren, a Senior Scientist at the Canadian Institutes for Health Research, is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes for Health Research.**

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